REMARKS

Applicants respectfully request reconsideration of the claims in view of the following remarks.

Claims 56 and 69-80 are pending.

While not acquiescing to any of the statements made by the examiner concerning the subject matter of claim 80, claim 80 has been cancelled without prejudice or disclaimer due to a restriction requirement by the Examiner. Applicants reserve the right to pursue the subject matter of this claim in one or more continuation applications.

Claims 58 and 78 have been amended and applicants submit the amendment is supported throughout the specification.

Interview Summary

Applicants thank Examiner Yao and Examiner Foley for the interview conducted on October 3, 2007. We discussed the enablement rejection.

Enablement

Claims 56 and 69-79 were rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. Applicants respectfully traverse the rejection.

1. The Office Action alleges the specification does not provide any guidance or objective evidence that inhibiting or neutralizing stanniocalcin in a mammal or tumor would effectively inhibit angiogenesis with concaminant reduction of tumor growth. The Examiner continues to assert that objective evidence such as a working example is necessary for enabling one skilled in the art to make and/or use the claimed invention. Applicants respectfully do not agree.

An enabling disclosure only requires a reasonable correlation to the scope of the claims. An example is not necessary if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice it without an undue amount of experimentation (MPEP § 2164.02). A substantial amount of experimentation is permissible if the experimentation is routine or if the specification provides a reasonable amount of guidance with

respect to the direction in which the experimentation should proceed. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) (emphasis added); see also *In re Angstadt*, 190 USPQ 214, 218 (CCPA 1976).

Applying these standards, Applicants submit the claims are enabled by the specification. A method of inhibiting angiogenesis as described by the specification is enabled, interalia, through the use of the art recognized model of angiogenesis, and has been confirmed by others. As discussed in the response filed on July 15, 2006 and April 11, 2007, one skilled in the art would expect based on Applicants' teachings and the knowledge in the art related to inhibition of angiogenesis with antibody antagonists that treatment with an agent that antagonizes stanniocalcin activity would inhibit angiogenesis. Applicants teach, for example, that neutralizing antibodies to stanniocalcin are useful as therapeutic molecules because they bind to stanniocalcin and thereby inhibit stanniocalcin activity (page 25, lines 17-19). Applicants show that expression of stanniocalcin was upregulated in endothelial cells undergoing tube formation. See, for example, specification at page 123, line 27.

In addition, Applicants have shown that stanniocalcin is expressed in ductal mammary adenocarcinoma, squamous cell carcinoma, chrondosarcoma, and renal cell carcinoma vasculature. Stanniocalcin is not expressed in normal vessels. See the specification at page 145, line 32 to page 146, line 7 and Figures 28 and 29. The combination of increased expression in endothelial cells, increased expression in tumor tissue and release of stanniocalcin during tube formation provides a reasonable correlation of the relationship of upregulation of stanniocalcin with angiogenesis in tumor tissues. Applicants submit that treating a tumor with an antagonist to stanniocalcin is enabled by this description and working examples and can occur by multiple routes of administration including intratumoral administration.

Applicants' teachings are also confirmed by other research in the field. For example, Filvaroff *et al.* found that overexpression of stanniocalcin 1 in mice leads to an increase in vascularity *in vivo*. In addition, McCudden et al. has shown that STC-1 and its receptor co-localized in breast cancer cells in 91% of cases (McCudden et al., *Mol. Cell. Endocrinol.*, 213:167 (2004), copy previously submitted). STC-1 was localized in invasive and ductal carcinoma in situ using an antibody to STC-1. STC-1 mRNA was detected in breast cancer cells by *in situ* hybridization and correlates with primary tumor size, number of positive lymph nodes, and stage of the cancer cell. (Wascher et al., *Clinical Cancer Res.*, 4:1427 (2003); copy previously submitted). Stanniocalcin is also induced in human tumor cells, such as colon

carcinoma, nasopharyngeal cancer, and ovarian cancer cultured under hypoxic conditions (Yeung et al, Endocrinology146.4951(2005))). Therefore, one skilled in the art would have had a reasonable expectation that neutralizing or inhibiting antibodies to stanniocalcin would be useful for inhibiting angiogenesis in tumors (page 12, lines 23-28 of the specification). The cited references show a correlation of upregulated expression of stanniocalcin in a wide variety of tumor types.

In addition, two other references provide additional confirmatory evidence. In Kahn et al, in an endothelial tube cell model , stanniocalcin was upregulated from the start of initial tube formation through full formation of the tubes (48 hours) as measured using the gene calling method and reverse transcriptase polymerase chain reaction. (Kahn et al, AJP156:1887, 2000; previously submitted).When tube formation was inhibited using a PPAR ligand, 15d-PGJ2, the expression level of stanniocalcin was decreased. See Table 4 in Kahn et al. A correlation of a decrease in expression with inhibition of tube formation is evidence in further support that inhibition of angiogenesis is correlated with inhibition of stanniocalcin.

The Gerritsen et al. reference studied gene expression using three different in vitro angiogenic models:HGF and VEGF in collagen gel; PMA, VEGF, and BFGF in collagen gel ; and PMA, VEGF, bFGF in fibrin gel. (Gerritsen et al, Physiol. Genomics10:13 (2002) Stably induced genes from each of these three models were identified and compared. Stanniocalcin was identified as one of the genes whose expression was upregulated in all three models and was stably upregulated through tube formation (48 hours) See figure 3 A. Gene expression was also compared in colon tumor samples as compared to normal tissue, and stanniocalcin was found to be one of the most highly upregulated genes in colon tissue. See figure 3 B Stanniocalcin was further evaluated for its role in angiogenesis in VEGF corneal tissue and expression in VEGF treated eyes was found to be dramatically higher. Stanniocalcin expression was also shown in colon adenocarcinomas by insitu hybridization. See Figure 5.

Applicants submit that the evidence in the specification, as well as confirmatory evidence in the art shows that the specification enables the full scope of the claimed subject matter. A number of different angiogenic and different actual tumor tissue samples all consistently show a correlation between angiogenesis and the upregulation of expression of stanniocalcin in endothelial cells undergoing angiogenesis and in a number of different tumor types including

breast carcinoma, and colon carcinoma. Applicants request withdrawal of the rejection on this basis.

2. Citing Mook et al., the Office Action alleges the use of therapeutic antibodies to inhibit disorders associated with angiogenesis is highly unpredictable. Applicants respectfully do not agree.

Mook discloses in preclinical animal experiments that inhibitors of MMP reduce cancer progression and metastasis. The inhibitors were not as effective in human clinical trials. However, the human trials were performed on patients with advanced stages of cancer and the animal experiments showed that MMP inhibitors are effective but only when they are administered in early stages of tumor development. See Mook at page 85, second column. Mook therefore does not teach that inhibition of angiogenesis is highly unpredictable.

As discussed in the response filed on July 15, 2006 and April 11, 2007, several anti-VEGF antibodies were known to inhibit angiogenesis both *in vitro* and *in vivo* and have been approved by the FDA for treating cancer. By 2004, the success of anti-angiogenesis agents, including antibody antagonists, in treating cancer prompted the FDA commissioner to state that antiangiogenesis therapy is the fourth modality of cancer treatment, the other three modalities being surgery, radiation, and chemotherapy. See, Folkman, 2007, *Comm. Oncol.*, 4:296-298 (copy enclosed). As of May 2007, nine angiogenic inhibitors were approved by the FDA and in more than 30 other countries to treat cancer. At least 50 other angiogenic inhibitors with varying degrees of antiangiogenic activity are in phase II and phase III clinical trials. Therefore, in view of Applicants' teachings and the knowledge in the art related to the inhibition of angiogenesis, one skilled in the art would expect that treatment with an agent that antagonizes stanniocalcin activity would inhibit angiogenesis.

3. Citing Dillman and Weiner, the Office Action alleges pharmaceutical administration of antibodies for the treatment of tumor requires a high degree of guidance as those skilled in the art recognize the unpredictability of treating mammals with antibodies. Applicants respectfully do not agree.

Dillman was published in 1989 approximately 10 years before the filing date of the application and therefore does not represent the state of the art at the time of filing. Weiner identifies obstacles to antibody therapy, such as tumor penetration, human anti-mouse antibody

(HAMA) response, and biodistribution. However, methods for enhancing antibody tumor penetration and biodistribution and reducing HAMA response were known at the time of filing of the present application. Weiner itself discloses that the majority of HAMA responses are directed toward the Fc domain of IgG molecule and that antibody fragments such as $F(ab')_2$, Fab, and Fv fragments which do not contain an Fc domain can be used instead. Colcher et al., for example, describe methods to genetically engineer monoclonal Fv antibody fragments, including single chain antibody variable region (Fv), multi-valent single chain Fv constructs, multimeric noncovalent scFv, mulitmeric covalent scFv, and engineered multimeric scFv (*QJ Nucl. Med.*, 42:225-241, 1998). Colcher et al. demonstrated that the smaller size of the Fv fragments allows for better tumor penetration and showed that antibody fragments accumulate in tumors. Using human adenocarcinomas expressing tumor-associated mucin, TAG-72, as a model for biodistribution studies in xenograft mice, blood ratios of anti-TAG-72 (CC49) scFv, Fab', $F(ab')_2$, and $(scFv)_2$ increased in tumor over time (Table II at page 234). The antibody fragments exhibited a much higher tumor:blood ratio at 24 and 48 hrs than IgG (Table IV at page 235). Eccles also discloses that antibody penetration into solid tumors can be improved by removing the constant (Fc) region and preparing monomeric or dimeric antibody fragments such as Fab, $F(ab')_2$, and scFV (*Breast Can. Res.*, 3:86-90, 2000 at page 87).

Applicants describe such antibody fragments and methods for making the fragments in the specification, for example, at page 41, lines 28 to page 42, line 18, page 42, line 26 to page 43, line 5, page 88, lines 5-7 and 11-14, and page 90, line 22 to page 91, line 22. In view of the teachings of the specification and the skill and knowledge in the art, as evidenced by Mook, Colcher et al., and Eccles, Applicants submit one of skill in the art would have reasonably expected that antibodies and fragments thereof that bind stanniocalcin would be useful for inhibiting angiogenesis in a tumor.

4. Citing Gura, the Office Action alleges extrapolating from *in vitro* to in *vivo* protocols is unreliable. Applicants respectfully do not agree.

If the art is such that a particular model is recognized as correlating to a specific condition, then the model should be accepted as correlating unless the Examiner has evidence that the model does not correlate. *In re Brana*, 34 USPQ2d, 1436, 1441 (Fed. Cir. 1995); MPEP § 2164.02. A rigorous or an invariable exact correlation is not required. *Cross v. Iizuka,* 244

USPQ, 739, 747 (Fed. Cir. 1985). The Office Action has failed to provide any evidence that the human endothelial model for tube formation does not correlate to angiogenesis. While Gura generally suggests that xenograft models are not predictive, Gura also confirms that human cell culture models are more reliable. See Gura at page 1042. Gura therefore does not suggest that the human endothelial cell model for tube formation does not correlate to angiogenesis.

Applicants have provided a working example showing upregulation of stanniocalcin precursor in human endothelial cells undergoing tube formation. The human endothelial cell model for tube formation is an art recognized model for angiogenesis. See, for example, Gerritsen et al, cited supra. Applicants teach that stanniocalcin precursor expression is dramatically enhanced under tube-forming conditions (*see*, Example 19, page 142 of the specification and page 25, lines 20-26 of the specification). In contrast, lower levels of stanniocalcin precursor are expressed under conditions that do not foster tube formation. Applicants contend this data demonstrates a strong correlation between expression of stanniocalcin and tube-formation.

Moreover, the involvement of stanniocalcin in angiogenesis is confirmed by others. For example, Filvaroff *et al.* found that stanniocalcin 1 transgenic mice had significantly higher capillary density in organs and muscles compared with age-matched wildtype littermates (*see*, Filvaroff *et al.*, 2002, *Endocrinology* 143(9):3681-3690, page 3689, first column, third paragraph). Filvaroff *et al.* also found that stanniocalcin 1 transgenic mice showed a larger increase in vascularity after femoral ligation compared to wildtype littermates. Thus, overexpression of stanniocalcin 1 leads to an increase in vascularity *in vivo*. This data further supports involvement of stanniocalcin in angiogenesis.

5. The Office Action maintains that *in vitro* results do not "guarantee" that one of skill in the art can inhibit angiogenesis by administering an antibody. The Office Action also emphasizes that major obstacles to "clinical efficacy" exist further extending the unpredictability of the claimed treatment, and that while thousands of drugs have shown activity in cell or animal models, only 39 that are used exclusively for chemotherapy have won FDA approval. Applicants submit that the Office Action is requiring Applicants to establish enablement to a higher degree of certainty than is required. The significant emphasis by the Examiner on the lack of clinical efficacy and alleged inability of the specification to guarantee success in vivo, in effect is requiring clinical data to establish enablement.

As discussed above, an enabling disclosure only requires a reasonable correlation to the scope of the claims. Clinical safety and efficacy is not the standard by which patentability is assessed. Considerations made by the FDA in determining safety and efficacy in the context of a clinical trial are different from those made by the PTO in determining whether a claim is enabled (MPEP § 2164.05). Therefore, the lack of FDA approval of therapeutics for treating a disease, such as cancer, has no bearing on enablement.

In view of the forgoing, Applicants submit the specification sufficiently teaches how to practice the claimed methods without undue experimentation. Withdrawal of the rejection is respectfully requested.

Summary

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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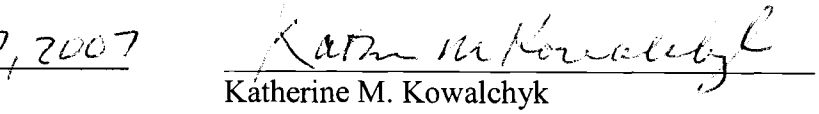

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